REMARKS

Claims 1-15 are pending. In the previous Office Action, the Examiner requested election of one of a species A-E, and indicated that claims 7-9 read on species A, and that claims 1-6 and 10-15 are generic. In response thereto, Applicants elected species A, and noted that the claims readable on the elected species are claims 1-15.

In the present Office Action, however, the Examiner indicated that only claims 1-7 and 10-15 read on the elected species. Applicants respectfully disagree and request clarification of the same in the next action. Claims 8 and 9 are not directed to the other species delineated. Indeed, claim 8 depends from claim 7; claim 9 depends from claim 8.

Applicants note with appreciation the Examiner's statement that the claims will also be examined for the genus.

Preliminarily, the Examiner objected to an informality in the specification, the absence of an abstract on a separate sheet, and an allegedly improper multiple dependent claim (claim 15 depending from claim 3). Applicants have corrected the informality in the specification and have submitted an abstract herein on a separate sheet. Applicants note, however, that claim 15 is not an improper multiple dependent claim. Claim 3 was previously amended to depend from Claim 1 only.

Rejections Under 35 U.S.C. § 102(b)

Claims 1-7 and 10-13, and 15 were rejected as allegedly anticipated by Rhind et al. (EP 0,384,624 or WO 90/09195, cited on form 1449). The Examiner asserted that Rhind et al. teach the coupling of two reduced Fab'SH fragments via a cross-linking

agent which has a maleimidyl group at each end thereof. The Examiner further asserted that, when the polymer recitation in claim 1 is read with the broadest definition contemplated by the applicant (citing pages 6-7 of the specification), claim 1 is "consistent with what is shown by Rhind et al." Applicants respectfully submit that "consistent with" is not the standard for anticipation. Rather, the standard for anticipation is the presence of each and every limitation of the claim either expressly or inherently in a piece of prior art. "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." MPEP 2131, citing, *inter alia*, Verdegaal *Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Under the correct standard, as discussed below, the Rhind et al. reference fails to anticipate claim 1. As claims 2-7 and 10-13 and 15 ultimately depend from claim 1, the Rhind et al. reference similarly fails to anticipate these claims as well.

Claim 1 as amended herein recites that the polymer molecule is "effective for increasing the circulating half-life of said fragment." Support for this recitation can be found, *inter alia*, on page 2, lines 1-14, in Table 2, and in Figure 5 of the specification as filed, wherein it is shown that one such polymer according to the invention, polyethylene glycol, **increases** the circulating half-life of the antibody fragments to which it is attached.

This limitation is not disclosed or suggested in Rhind et al. Indeed, Rhind et al. discusses attaching reporter or effector molecules that have "good blood clearance,"

resulting in high tumour:blood and tumour:bone (see, for example, page 1 of WO 90/09195). For the tumour:blood to be high, the molecules would have to be cleared from the blood quickly, i.e., the circulating half-life is decreased.

Applicants respectfully request that this rejection be withdrawn.

Claims 1-3, 7, 10-13, and 15 were rejected as allegedly anticipated by Huston et al. (5,534,254). Applicants respectfully traverse this rejection.

Claim 1, from which all the foregoing claims ultimately depend, recites that the polymer molecule is "effective for increasing the circulating half-life of said fragment." Huston et al. does not disclose or suggest such a polymer. As acknowledged by the Examiner, Huston et al. describes hexane linkers and peptide linkers, neither of which is a polymer effective for increasing circulating half-life. Indeed, as acknowledged by the Examiner, Huston et al. teaches achieving accelerated clearance rates (*see* June 4, 2003 Office Action, page 7).

Applicants respectfully request that this rejection be withdrawn.

Rejections Under 35 U.S.C. § 103(a)

Claims 1 and 13-14 were rejected as allegedly unpatentable over Rhind et al. or Huston et al., further in view of Akita et al. (5,968,511). The Examiner relied upon the teachings of Rhind et al. and Huston et al. as applied to claims 1 and 13 above. The Examiner relied upon Akita et al. for allegedly teaching multispecific antibodies, and concluded that the term "cytotoxic agent" recited in Akita et al. would encompass TNF-alpha.

First, as discussed above, discussion incorporated herein, neither Rhind et al. nor Huston et al. disclose or suggest the polymer as presently claimed. Akita et al. does not overcome this deficiency. Therefore, claims 1 and 13-14 cannot be obvious over Rhind et al. or Huston et al. in view of Akita et al.

Further, although Akita et al. does describe bispecific antibodies to localize cytotoxic agents to cells that express ErbB3 (col. 14, lines 39-58), TNF-alpha is not one of the cytotoxic agents listed. Rather, TNF-alpha is listed as a "cytokine" (see col. 9, line 22). It is respectfully submitted that the Examiner is using impermissible hindsight to reconstruct Applicants' invention in maintaining this rejection. MPEP § 2141, citing *Hodosh v. Block Drug Co., Inc.*, 786 F.2d 1136, 1143 n.5, 229 USPQ 182, 187 n.5 (Fed. Cir. 1986).

Applicants respectfully request that this rejection be withdrawn.

Claims 1 and 13-14 were rejected as allegedly unpatentable over Huston et al. in view of Barbanti et al. (5,436,154). The Examiner relied upon Huston et al. for allegedly teaching that "sFv constructs have superior in vivo pharmacokinetic properties (accelerated distribution and clearance rates) over F(ab)2 dimers." (June 4, 2003 Office Action, page 7.) The Examiner relied upon Barbanti et al. for allegedly teaching antibodies to TNF-alpha, and F(ab')2 fragments thereof. The Examiner concluded that

> [s]ince Huston et al. teach that dimeric sFv constructs clear even mere [sic] rapidly than F(ab')2 fragments, it would have been obvious to provide a dimeric sFv construct

> specific for TNF-alpha to conduct the therapeutic treatments taught by Barbanti et al.

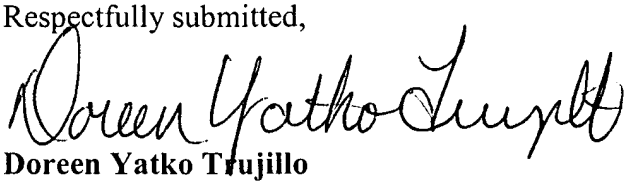
(June 4, 2003 Office Action, page 7.) From the foregoing passage, it appears that the Examiner considers Applicants' invention to be directed to increasing the clearance rate, i.e., decreasing the circulating half-life, of antibody fragments. Applicants respectfully submit that the Examiner is misapprehending Applicants' invention. As discussed above, discussion incorporated herein, claim 1 has been amended to recite that the polymer molecule is "effective for **increasing** the circulating half-life of said fragment."

Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

Applicants respectfully submit that the above-identified application is now in condition for allowance and request early notification of the same.

Respectfully submitted,



Doreen Yatko Trujillo
Registration No. 35,719

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COZEN O'CONNOR, P.C.
1900 Market Street, 6th Floor
Philadelphia, PA 19103-3508
Telephone: (215) 665-5593
Facsimile: (215) 701-2005